

Applicants: Marc Feldmann, Ravinder N. Maini and
Richard O. Williams
Serial No.: Not Yet Known
Filed: January 20, 2004
Page 5

REMARKS

By this Preliminary Amendment, applicants have amended the specification, and canceled claims 1-22 and 31-45, without prejudice. Accordingly, upon entry of this Preliminary Amendment, claims 23-30 will be pending in the subject application.

Information Disclosure Statement

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following references which are listed on the PTO-1449 form attached hereto as **EXHIBIT A**.

1. U.S. Patent No. 5,672,347, issued September 30, 1997 (Aggarwal et al.);
2. U.S. Patent No. 5,317,019, issued May 31, 1994 (Bender et al.);
3. U.S. Patent No. 4,695,459, issued September 22, 1987 (Steinman et al.);
4. U.S. Patent No. 5,502,066, issued March 26, 1996 (Heinemann et al.);
5. U.S. Patent No. 5,580,873, issued December 3, 1996 (Bianco et al.);

Applicants: Marc Feldmann, Ravinder N. Maini and
Richard O. Williams
Serial No.: Not Yet Known
Filed: January 20, 2004
Page 6

6. U.S. Patent No. 5,656,272, issued August 12, 1997 (Le et al.);
7. U.S. Patent No. 5,204,329, issued April 20, 1993 (Ackerman et al.);
8. U.S. Patent No. 5,698,195, issued December 16, 1997 (Le et al.);
9. U.S. Patent No. 5,919,452, issued July 6, 1999 (Le et al.);
10. U.S. Patent No. 5,795,967, issued August 18, 1998 (Aggarwal et al.);
11. U.S. Patent No. 5,994,510, issued November 30, 1999 (Adair et al.);
12. U.S. Patent No. 5,096,906, issued March 17, 1992 (Mandell, et al.);
13. U.S. Patent No. 5,658,570, issued August 19, 1997 (Newman, et al.);
14. U.S. Patent No. 6,015,557, issued January 18, 2002 (Tobinick, et al.);
15. U.S. Patent No. 6,177,077, issued January 23, 2001 (Tobinick, et al.);

Applicants: Marc Feldmann, Ravinder N. Maini and
Richard O. Williams
Serial No.: Not Yet Known
Filed: January 20, 2004
Page 7

16. U.S. Patent No. 5,958,413, issued September 28, 1999, (Anagnostopulos, et al.);
17. U.S. Patent No. 6,190,691, issued February 20, 2001 (Mak);
18. U.S. Patent No. 5,298,396, issued March 29, 1994 (Kotzin, et al.);
19. U.S. Patent No. 5,468,481, issued November 21, 1995 (Sharma, et al.);
20. U.S. Patent No. 5,260,422, issued November 9, 1993 (Clark, et al.);
21. PCT International Application No. WO 89/08460, published September 21, 1989;
22. PCT International Application No. WO 92/08474, published May 29, 1992;
23. PCT International Application No. WO 92/07585, published May 14, 1992;
24. PCT International Application No. WO 98/24463, published June 11, 1998;
25. PCT International Application Publication No. WO 92/07076, published April 30, 1992;

Applicants: Marc Feldmann, Ravinder N. Maini and
Richard O. Williams
Serial No.: Not Yet Known
Filed: January 20, 2004
Page 8

26. PCT International Application Publication No.
WO 91/10722, published July 25, 1991;
27. PCT International Application Publication No.
WO 90/15152, published December 13, 1990;
28. PCT International Application Publication No.
WO 92/16553, published October 24, 1996;
29. PCT International Application Publication No.
WO 95/09652, published April 13, 1995;
30. PCT International Application Publication No.
WO 96/33204, published October 24, 1996;
31. PCT International Application Publication No.
WO 00/50079, published August 31, 2000;
32. European Patent Application No. EP 0 240 344,
published October 7, 1987;
33. Australian Patent Application No. AS 58976/90,
published September 22, 1987;
34. Canadian Patent No. 2,021,369, issued January
19, 1991;
35. German Patent No. DE 40 06 269 A1, issued
February 28, 1990;
36. British Patent Application No. GB 2 246 569 A,
published June 15, 1990;

37. Horneff, G., et al., "Elevated levels of circulating tumor necrosis factor- α , interferon- γ , and interleukin-2 in systemic reactions induced by anti-CD4 therapy in patients with rheumatoid arthritis", Cytokine, 3(3):266-247 (1991);
38. Brennan, F., et al. "Inhibitory effect of TNF α antibodies on synovial cell interleukin-1 production in rheumatoid arthritis", The Lancet, 2(8657):244-247 (1989);
39. Steinbrüchel, D., et al., "Monoclonal antibody treatment (anti-CD4 and anti-interleukin-2 receptor) combined with cyclosporine A has a positive but not simple dose-dependent effect on rat renal allograft survival", Scandinavian J. Immunol., 34(5):627-633 (1991);
40. Breedveld, F., et al., "Anti-CD4 antibodies in rheumatoid arthritis", Clin. Experimental Rheum., 10(4):325-326 (1992);
41. Brennan, F., et al., "TNF α - a pivotal role in rheumatoid arthritis?", British J. Rheumatology, 31(5):293-298 (1992);
42. Elliott, M.J., et al., "Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to TNF- α : safety, clinical efficacy and control

of the acute phase response", Cell. Biochemistry, Supplement, 0(17B):145 (1993);
Abstract EZ405;

43. Williams, R.O., et al., "Synergy between anti-CD4 and anti-tumor necrosis factor in the amelioration of established collagen-induced arthritis", Proc. Natl. Acad. Sci. USA, 91:2762-2766 (1994);
44. Ralph, P., "Clinical and Preclinical Studies Presented at the Keystone Symposium on Arthritis, Related Diseases, and Cytokines", Lymphokine Cytokine Research, 12(4):261-263 (1993);
45. Racadot, E., "Immunological follow-up of 17 patients with rheumatoid arthritis treated in vivo with an anti-T CD4+ monoclonal antibody (B-F5)", Clinical Experimental Rheumatology, 10:365-374 (1992);
46. Williams, R.O., et al., "Successful therapy of collagen-induced arthritis with TNF receptor-IgG fusion protein and combination with anti-CD4", Immunology, 84:433-439 (March 1995);
47. Van Der Lubbe, P.A., et al., "A Randomized, Double-Blind, Placebo-Controlled Study of CD4 Monoclonal Antibody Therapy In Early Rheumatoid Arthritis", Arth. Rheuma., 38(8):1097-1106 (1995);

48. Choy, E.H.S., et al., "Therapeutic Monoclonal Antibodies", British J. Rheumatology, 34:707-715 (1995);
49. Rankin, E.C.C., et al., "The Therapeutic Effects of an Engineered Human Anti-Tumor Necrosis Factor Alpha Antibody (CDP571) in Rheumatoid Arthritis", British J. Rheumatology, 34:334-342 (1995);
50. Butler, D.M., et al., "Modulation of proinflammatory cytokine release in rheumatoid synovial membrane cell cultures. Comparison of monoclonal anti TNF- α antibody with the interleukin-1 receptor antagonist", Eur. Cytokine Netw., 6(4):225-230 (1995);
51. Horneff, G., et al., "Treatment of Rheumatoid Arthritis with an Anti-CD4 Monoclonal Antibody", Arth. Rheumatism, 34(2):129-140 (1991);
52. Van Dulleman, H.M., et al., "Treatment of Crohn's Disease With Anti-Tumor Necrosis Factor Chimeric Monoclonal Antibody (cA2)", Gastroenterology, 109(1):129-135 (1995);
53. Watts, R.A., and Issacs, J.D., "Immunotherapy of rheumatoid arthritis", Annals Rheumatic Diseases, 51:577-579 (1992);

54. Schacht, E., "Gegernwärtige und zukünftige Therapiestrategien der rheumatoiden Arthritis (RA) ["The current and future therapy strategies of rheumatoid arthritis (RA)"], Zeitschrift für Rheumatologie, 52(6):365-382 (1993);
55. Elliott, M.J., et al., "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to TNF α ", Rev. Esp. Reumatol., 20 (Suppl. 1):148 (1993); Abstract 320;
56. Natanson, C., et al., "Selected Treatment Strategies for Septic Shock Based on Proposed Mechanism of Pathogenesis", Annals Internal Med., 120(9):771-783 (1994);
57. Hervé, P., et al., "Phase I-II Trial of a Monoclonal Anti-Tumor Necrosis α Factor Antibody for the Treatment of Refractory Severe Acute Graft-Versus-Host Disease", Blood, 79(12):3362-3368 (1992);
58. Thorbecke, G.J., et al., "Involvement of endogenous tumor necrosis factor α and transforming growth factor β during induction of collagen type II arthritis in mice", Proc. Natl. Acad. Sci. USA, 89:7375-7379 (1992);
59. Piguet, P.F., et al., "Evolution of collagen arthritis in mice is arrested by treatment with anti-tumor necrosis factor (TNF) antibody or a

recombinant soluble TNF receptor", Immunology,
77:510-514 (1992);

60. Brahn, E., et al., "Effects of Tumor Necrosis Factor and Combination Cyclosporin A/Methotrexate Therapy on Collagen Arthritis", Arthritis Rheum., 32(4 Suppl.) S133 (1989); Abstract D42;
61. Markowitz, J., et al., "Immunology of Inflammatory Bowel Disease: Summary of the Proceedings of the Subcommittee on Immunosuppressive Use in IBD", J. Ped. Gastroenterology Nutrition, 12:411-423 (1991);
62. Cohen, S., et al., "Comparison of the Safety and Efficacy of Cyclosporine-A and Methotrexate in Refractory Rheumatoid Arthritis: A Randomized, Multi-Centered, Placebo-Controlled Trial", Rev. Esp. Reumatol., 20 (Suppl. 1):148 (1993); Abstract 318;
63. Pascalis, L., et al., "Longterm Efficacy and Toxicity of Combined Cyclosporine A-Steroid-Methotrexate Treatment in Rheumatoid Arthritis", Rev. Esp. Reumatol., 20 (Suppl. 1):148 (1993); Abstract 319;
64. Arend, W.P., et al. (1990) Arthritis Rheum., 33(3):305-315;
65. Bach, J.F. (1993) TiPs, 14:213-216;

66. Barrera, P., et al. (1995) Br. J. Rheumatol., 34:747-755;
67. Barrera, P. (1995) Cytokine, 3(5):504 (Abstract 330);
68. Bologna, C., et al. (1996) Presse Med., 25:876-878, XP002048553;
69. Borigini, M.J., et al. (1995) Baillière's Clin. Rheum., 9(4):689-710;
70. Brennan, et al. (1994) Clin. Exp. Immunol., 97:1-3;
71. Cooper, K.D. (1993) Clin. Rev. Allergy, 11:543-559;
72. Debets, et al. (1994) Immunology Today, 15:455-458;
73. Elliott, M.J., et al. (1993) Arth. Rheum., 36(12):1681-1690;
74. Elliott, M.J., et al. (1994) Int. Arch. Allergy Immunol., 104:112-125;
75. Elliott, M.J., et al. (1994) Lancet, 344:1105-1110;

76. Elliott, M.J., et al. (1994) Lancet, 344:1125-1127;
77. Feldmann, M., et al. (1996) Ann. Rev. Immunol., 14:397-440;
78. Fries, J.F., et al. (1990) J. Rheumatol., 17(22):12-15;
79. Genzyme Catalog, (1991) pp. 79-80;
80. Harris, et al. (1993) Tibtech, 11:42-44;
81. Herzog, C., et al. (1987) Lancet, 2(8573):1461-1462;
82. Hozzof, et al. (1987) Lancet, 11:1461-1462;
83. Kahan, B.D. (1992) Curr. Opin. Immunol., 4:553-560;
84. Kalden, J.R., et al. (1995) Curr. Opin. Rheum., 7:(3)191-197;
85. Kalden, J.R., et al. (1997) Curr. Opin. Rheum., 9:206-212;
86. Kavanaugh, et al. (1996) Arth. Rheum., 39(9):18-22 (Abstract 575);
87. Kozarek (1989) Ann. Int. Med., 110:353-356;

88. Littman, B.H., et al. (1995) Arthritis Rheum.,
38:29-37;
89. Maini, R.N. (1996) J. Royal College of
Physicians of London, 30(4):344-351;
90. Maini, R.N. (1995) Arth. Rheum., Suppl.
38(9):S186 (Abstract 200);
91. Matsumiya, G., et al. (1996) Transplant
Proceed., 28(2):751-753;
92. Moreland, L.W., et al. (1995) Arthritis Rheum.,
38:1581-1588;
93. Moreland, L.W., et al. (1996) J. Rheumatol.,
(Suppl. 44) 23:78-83;
94. Paul, W.E. (1993) Fundamental Immunology, 3rd
edition, Raven Press, NY, pp. 807-812;
95. Paul, W.E. (1993) Fundamental Immunology, 3rd
edition, Raven Press, NY, p. 242;
96. Qin, S., et al. (1987) Eur. J. Immunol.,
17:1159-1165;
97. Richardson, C., et al. (1995) Br. J. Clin.
Prac., 49:135-139;

Applicants: Marc Feldmann, Ravinder N. Maini and
Richard O. Williams
Serial No.: Not Yet Known
Filed: January 20, 2004
Page 17

98. Sander, O., et al. (1995) Arthritis Rheum.,
38:S266 (Abstract 678);
99. Sosman, J.A., et al. (1993) J. Pediatric
Hematol. Oncol., 15(2):185-195;
100. Stein, C.M., et al. (1994) Arthritis Rheum.,
37:S252;
101. Strober, et al. (1990) Immunol. Reviews,
118:233-255;
102. Stuart, et al. (1986) Laboratory Investigation,
34:1-13;
103. Waldmann, T.A. (1991) Science, 252:1657-1662;
104. Weinblatt, M.E., et al. (1994) Arthritis Rheum.,
37:1492-1498; and
105. Williams, R.O., et al. (1995) Immunology,
84:433-439.

This application is a divisional of U.S. Serial No. 09/093,450, filed June 8, 1998, which is a continuation of U.S. Serial No. 08/607,419, now abandoned, filed February 28, 1996, which is a continuation-in-part of U.S. Serial No. 08/403,785, filed May 3, 1995, now U.S. Patent No. 5,741,488, issued April 21, 1998, based on PCT International Application No. PCT/GB93/0207, filed October 6, 1993, which is a continuation-in-part of U.S.

Applicants: Marc Feldmann, Ravinder N. Maini and
Richard O. Williams
Serial No.: Not Yet Known
Filed: January 20, 2004
Page 18

Serial No. 07/958,248, filed October 8, 1992, now abandoned.

The above listed references 1-6, 21-23 and 37-63 were submitted to the U.S. Patent and Trademark Office in an Information Disclosure Statement filed on June 23, 1998 in connection with U.S. Serial No. 09/093,450, to which priority under 35 U.S.C. §120 is claimed. The above listed reference 24 was submitted to the U.S. Patent and Trademark Office in a Supplemental Information Disclosure Statement filed on July 14, 1998 in connection with U.S. Serial No. 09/093,450, to which priority under 35 U.S.C. §120 is claimed. The above listed reference 7 was cited by the U.S. Patent and Trademark Office in a Notice of References Cited issued in a July 20, 1999 Office Action in connection with U.S. Serial No. 09/093,450, to which priority under 35 U.S.C. §120 is claimed. The above listed references 8-11 were submitted to the U.S. Patent and Trademark Office in a Supplemental Information Disclosure Statement filed on January 20, 2000 in connection with U.S. Serial No. 09/093,450, to which priority under 35 U.S.C. §120 is claimed. The above listed references 12-20, 25-36 and 64-105 were submitted to the U.S. Patent and Trademark Office in a Supplemental Information Disclosure Statement filed on June 27, 2003 in connection with U.S. Serial No. 09/093,450, to which priority under 35 U.S.C. §120 is claimed. According to 37 C.F.R. §1.98(d), copies of these references are not required to be provided to the Patent and Trademark Office since they were previously submitted to, or cited by, the Patent and Trademark Office in an application relied upon for an earlier filing date under 35 U.S.C.

Applicants: Marc Feldmann, Ravinder N. Maini and
Richard O. Williams
Serial No.: Not Yet Known
Filed: January 20, 2004
Page 19

\$120. Accordingly, copies of references 1-105 are not attached to this Information Disclosure Statement.

No fee, other than the enclosed \$770.00 application filing fee, is deemed necessary in connection with the filing of this Preliminary Amendment and Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400